Original Article

Pretreatment volumetric parameters of FDG-PET predict the survival after Yttrium-90 radio-embolization in metastatic liver disease

Siavash Mehdizadeh Seraj1, Mahdi Zirakchian Zadeh1,2, Thomas J Werner1, Hongming Zhuang2, Terence Gade1, Abass Alavi1, Stephen J Hunt1

1Department of Radiology, Hospital of University of Pennsylvania, PA, USA; 2Department of Radiology, Children’s Hospital of Philadelphia, PA, USA

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Abstract: This study aimed to determine the prognostic value of pretreatment FDG-PET in patients with metastatic liver disease undergoing Yttrium 90 (90Y) radio-embolization using global disease assessment measures. Data from 16 patients with metastatic liver disease (8 males, 8 females) aged 55-97 years (mean: 67±12) were retrospectively collected. On PET, active malignant lesions in the liver were segmented with an adaptive thresholding system (ROVER software, ABX GmbH, Radeberg, Germany). Conventional measures of PET quantification such as SUVmean, SUVmax, and partial volume-corrected SUVmean (pvcSUVmean) and volumetric parameters including metabolic tumor volume (MTV), total lesion glycolysis (TLG) and pvcTLG were measured. Receiver operating characteristic (ROC) was used to determine the optimal cutoffs for Kaplan-Meier analyses. Kaplan-Meier analysis was performed to estimate progression-free survival (PFS) and overall survival (OS). In addition, Cox regression analysis was used to determine predictors of PFS and OS. There was no correlation between pretreatment conventional parameters of FDG-PET and PFS or OS. In contrast, in the univariate Cox regression analyses, pretreatment volumetric parameters were significant predictors for PFS [(TLG (HR: 6.1, \(P=0.02\)), pvcTLG (HR: 3.9, \(P=0.03\)) and MTV (HR: 5.8, \(P=0.02\))]. Moreover, TLG (HR: 6.1, \(P=0.03\)), pvcTLG (HR: 5.2, \(P<0.01\)) and MTV (HR: 10.7, \(P<0.01\)) were significant prognostic factors for OS. Pretreatment volumetric FDG-PET parameters are prognostic factors for PFS and OS in patients with liver metastasis receiving radio-embolization with 90Y.

Keywords: Pretreatment, FDG-PET, liver, metastases, Y-90, radioembolization, volumetric parameters, MTV, TLG, PvcTLG, survival

Introduction

Metastasis is the leading etiology of hepatic tumors and colorectal, lung, breast, and pancreatic cancers are the most frequent sources of metastases. In spite of remarkable advances in diagnosis and management, the prognosis of patients with hepatic metastases has remained poor. Radioembolization with Yttrium 90 (90Y) microspheres is increasingly used for unresectable hepatic metastases. 90Y microspheres occlude the blood supply to the tumor and provide high dose radiation to the tumor vasculature while sparing the adjacent normal tissue.

18F-fluorodeoxyglucose positron emission tomography (FDG-PET) is a key imaging modality in cancer diagnosis, staging, response evaluation, recurrence detection and prognosis [1-5].

Although, morphological assessment based on Response Evaluation Criteria In Solid Tumors (RECIST) is the gold standard for initial evaluation and response to treatment prediction [6], it has recently been shown that pretreatment metabolic behavior of hepatocellular carcinoma (HCC) as determined by FDG-PET/CT is superior to CT-based assessment using RECIST guidelines for evaluating survival outcome after 90Y radio-embolization [7]. However, the prognostic role of pre-treatment FDG-PET in metastatic hepatic tumors has not yet been well established.

Conventional methods of PET quantification are prone to misinterpretation of the overall dis-
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A single region of interest samples only a portion of the affected area which underestimates the true burden of the disease. Therefore, the concept of global disease measures of metabolic activity has been introduced for quantitative assessment of FDG-PET in various conditions (including malignancy), and the preliminary results appear to be promising [8-12]. Since the utilization of global disease assessment overcomes the shortcomings related to conventional approaches, we aimed to determine the prognostic value of pretreatment FDG-PET in patients with metastatic liver disease undergoing $^{90}$Y radio-embolization using such techniques.

Methods

Patient selection

In this retrospective study, we selected 16 patients (8 males and 8 females) who were treated with $^{90}$Y radio-embolization for metastatic liver disease. On average, FDG-PET scans were acquired approximately 3 months (range 0.5-6.4 months) before the date of radio-embolization. Approval for retrospective data collection along with Health Insurance Portability and Accountability (HIPAA) waiver were granted by the Institutional Review Board (IRB).

Image acquisition

FDG-PET scans were performed on integrated PET/CT scanners (Gemini TF; Philips Healthcare, The Netherlands). Blood glucose was measured prior to the FDG administration, and 15 mCi of FDG was administered intravenously after at least 8 hours of fasting if the blood glucose levels were below 200 (mg/dl). Whole body PET images were acquired 60 minutes following FDG administration and a low dose CT-scan was performed for attenuation correction.

Image analysis

A qualified physician evaluated the pretreatment FDG-PET scans, blinded to the patients' final outcome. All the scans were analyzed using an adaptive thresholding system (ROVER software; ABX GmbH, Radeberg, Germany) [13]. Spherical or cylindrical masks were placed over the active malignant lesions in the liver and the adaptive thresholding algorithm of ROVER delineated the boundaries of active lesions (Figure 1). Conventional quantitative PET parameters such as SUVmean and SUVmax were automatically computed by ROVER in addition to partial volume corrected pcvSUVmean calculated by the software's partial volume correction algorithm. Volumetric measures of global disease burden calculated by the ROVER software included: MTV, total lesion glycolysis (TLG = SUVmean × MTV), and partial volume corrected TLG (pcvTLG = pcvSUVmean × MTV). The reproducibility and accuracy of this approach has previously been verified and validated [9, 13-15].

Statistical analysis

Receiver operating characteristic (ROC) analysis was used to determine the optimal cut-off value for both conventional and volumetric parameters of tumor metabolic activity for predicting the outcome in the patients. Kaplan-Meier analysis was used to estimate progression-free survival (PFS) and overall survival (OS). Survivors were censored at the time of last contact. Univariate Cox regression analysis was performed to identify independent prognostic factors for PFS and OS. Statistical analysis was performed using SPSS Statistics version 24 (IBM corp, NY, USA). Statistical sig-
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Results

The study included 16 patients (mean age: 67±12, range 55 to 97 years) who underwent 90Y radio-embolization between August 2012 and February 2017. The demographic and clinical data of patients are provided in Table 1. At the time of analysis, 8 patients were deceased. The patients were followed-up for the median of 14 months (range 1.6-43.3 months). In Kaplan-Meier analysis, higher pretreatment volumetric parameters were associated with inferior PFS (median: 3.3 months for TLG≥87.2 vs 19.4 months for TLG<87.2, P=0.01; median: 3.3 months for pvcTLG≥299 vs 10.6 months for pvcTLG<299, P=0.02 and median: 2.7 months for MTV≥130.1 vs 9.5 months for MTV<130.1, P=0.01) (Figure 2). In addition, higher pretreatment volumetric measures of global disease activity were associated with inferior OS (median: 6.6 months survival for TLG≥275.9, P=0.01; median: 3.30 months for pvcTLG≥670.7, P<0.01 and median: 3.30 months for MTV≥75.5, P<0.01) (Figure 3). Since the groups with lower values than cutoffs did not cross the line y=0.5 in OS Kaplan-Meier analysis, the OS medians could not be determined. The Kaplan-Meier analyses did not show any significant correlation between PFS or OS and conventional PET parameters such as SUVmax and SUVmean. Even after applying partial volume correction to SUVmean (pvcSUVmean), we did not observe a statistically significant correlation.

Univariate Cox regression analysis showed that higher TLG, pvcTLG and MTV were significant predictor factors of PFS (TLG: HR: 6.1, P=0.02; pvcTLG: HR: 3.9, P=0.03 and MTV: HR: 5.8, P=0.02) (Table 2). In addition, higher pretreatment volumetric parameters were significant predictor factors for OS (TLG: HR: 6.1, P=0.03; pvcTLG: HR: 5.2, P<0.01 and MTV: HR: 10.7, P<0.01) (Table 3). The conventional parameters namely, SUVmax, SUVmean and pvcSUVmean could not predict the PFS or OS in the Cox regression analysis.

Discussion

Numerous attempts have been made to find a reliable tool that can inform interventionalists about the potential prognosis of patients being considered for 90Y radio-embolization of liver tumors [16]. At present, there is a dearth of objective criteria to assess likelihood of post-treatment survival prior to locoregional therapy, and both patients and clinicians are thus unable to reliably assess the real risk-benefit of the procedure. Even though FDG-PET has an established role in survival prediction for a variety of malignancies and treatment paradigms, limited data is available on the ability of this modality in survival prediction of patients undergoing 90Y radio-embolization [17]. In this study, the feasibility of pretreatment FDG-PET to predict the survival of patients with liver metastasis after 90Y radio-embolization was shown. Our results demonstrated that the volumetric FDG-PET parameters including MTV, TLG and pvcTLG were predictors of PFS and OS. The conventional PET parameters including SUVmax and SUVmean failed to anticipate OS or PFS.

Our findings were in line with other studies that evaluated the role of FDG-PET in outcome prediction of patients undergoing 90Y radioemboli-
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Jreige et al. investigated the capability of pretreatment FDG-PET to predict the survival of HCC patients undergoing radioembolization [7]. In their study, assessment based on FDG-PET was predictive for survival, whereas, assessment based on CT could not predict the survival outcome. Sabet et al. have demonstrated that early response assessment using FDG-PET is predictive of outcome in patients with liver metastasis and early metabolic responders survived longer than non-responders [19]. In a retrospective study, responses on FDG-PET/CT have been shown to significantly predict PFS, whereas tumor density and RECIST did not [20].

The concept of global metabolic activity was first introduced for the assessment of brain function in Alzheimer’s disease [22]. This approach allows assessment of global disease burden and is particularly useful in clinical oncology [23] where it has been effectively employed in lymphoma [8], mesothelioma [24] and lung cancer [25]. Over the past decade, the role of global volumetric PET parameters has been investigated in a variety of disorders, especially those related to malignancy [12, 13, 21, 26-32]. Results of these studies imply the superiority of volumetric parameters over conventional methods of PET quantification. MTV, which is the total volume of all active lesions observed on PET, has been shown to be prognostic in multiple myeloma [27] and non-small cell lung cancer [29, 32]. TLG is a unique index which is indicative of the global metabolic burden of disease, since it integrates the volumetric data with metabolic behavior of tumor. The parameter pvcTLG has an added value compared to TLG as it is corrected for partial volume effect, a phenomenon that degrades the accuracy of PET quantification [33-36] especially when measuring small lesions. Both TLG and pvcTLG have previously been shown to be independent prognostic factors in malignancies [12, 26, 32]. In our study, the volumetric parameters including MTV, TLG and pvcTLG significantly predicted PFS and OS. Similar to our results, a study by Fendler et. al showed that changes in MTV and TLG as measured by FDG-PET predicted the survival of colorectal cancer patients with hepatic metastases who had undergone 90Y radio-embolization, while SUVpeak and SUVmax changes as
well as the RECIST 1.1 criteria failed to predict survival [21]. The results of Fendler’s study support our findings, indicating the superiority of volumetric FDG-PET parameters derived from the global disease burden assessment. In contrast, conventional methods of PET quantification are not predictive of survival in patients with liver metastases.

Our study has several limitations. First, the present study is not designed to distinguish effects of the locoregional therapy on prognosis or survival. However, by reliably providing quantitative assessment of overall tumor burden and its relation to post-treatment survival in the setting of locoregional therapy, it can allow clinicians to better define patients with regards to those more likely or less likely to benefit from radio-embolization. Patients with a high-risk score may choose to forgo the invasive procedure given the uncertain benefit in the setting of their tumor burden. Additionally, we only assessed pretreatment scans since no follow-up scans were available to evaluate post treatment prognostic value. In addition, our study was limited by the heterogeneity of primary tumor diagnosis. A study population with a large sample size for each primary tumor subgroup is necessary to elucidate the role of pretreatment FDG-PET in different subgroups. Finally, only 16 subjects were evaluated, and further prospective studies with larger sample of patients are needed to validate our findings.

Conclusion

In conclusion, this study seeks to provide objective criteria to assess likelihood of post-treatment survival prior to locoregional therapy, to allow both patients and clinicians to better assess the real risk-benefit of the procedure. To our knowledge, this is the first study that showed the role of pretreatment FDG-PET using global disease assessment in predicting survival in patients with metastatic liver disease undergoing treatment with 90Y radio-embolization. Volumetric FDG-PET parameters including MTV, TLG and pvcTLG were predictive of patients’ outcome. Higher MTV, TLG and pvcTLG were associated with inferior PFS and OS. By comparison, the current conventional PET quantification measures (SUVmean and SUVmax) failed to predict PFS or OS.

Disclosure of conflict of interest

None.

Address correspondence to: Stephen J Hunt, Department of Radiology, Hospital of University of Pennsylvania, 3400 Spruce St, Philadelphia, PA 19104, USA. Tel: 215-615-3591; Fax: 215-615-3545; E-mail: stephen.hunt@uphs.upenn.edu

References


Table 2. PFS univariate Cox regression analysis for pretreatment global measurements

<table>
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<th>Parameter</th>
<th>HR</th>
<th>95% CI</th>
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<td>1.2-29.5</td>
<td>0.02</td>
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<td>pvcTLG</td>
<td>3.9</td>
<td>1.1-13.8</td>
<td>0.03</td>
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<td>MTV</td>
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Table 3. OS univariate Cox regression analysis for pretreatment volumetric measurements

<table>
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<th>Parameter</th>
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<th>P</th>
</tr>
</thead>
<tbody>
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<td>TLG</td>
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<td>1.1-32.9</td>
<td>0.03</td>
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<td>MTV</td>
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Predictive value of volumetric parameters


